the lymphatic vessels that distinguish this condition from other protein-losing disorders (eg, Crohn's and Whipple's diseases).

Treatment

Some patients improve on a low-fat diet (< 30 gm/day), supplements of medium-chain triglycerides, and occasionally by resection, if the lesion is localized.

INFECTION AND INFESTATION

For discussions of giardiasis, diphyllobothriasis, ascariasis, and hookworm disease, see Ch. 15.

Acute bacterial and viral infections may cause transient malabsorption, probably due to temporary, superficial damage to the villi and microvilli. Chronic bacterial infections of the small bowel are uncommon apart from blind loops and diverticula. Intestinal bacteria may utilize dietary vitamin B_{12}, perhaps interfere with enzyme systems, and cause areas of superficial inflammation.

---

57. CHRONIC INFLAMMATORY DISEASES OF THE BOWEL

A spectrum of inflammatory bowel disorders with overlapping clinical, epidemiologic, and pathologic findings but without a definite etiology. Both Crohn's disease **(CD)** and ulcerative colitis (see below) are characterized by chronic inflammation at various sites in the GI tract. Certain differences in disease patterns justify a distinction at least between ulcerative colitis and CD, although groupings and subgroupings are somewhat artificial. Some cases will be difficult, if not impossible, to classify.

CROHN'S DISEASE (CD)

(Regional Enteritis; Granulomatous Ileitis or Ileocolitis)

A nonspecific chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may also occur in any part of the GI tract from the mouth to the anus and perianal area.

Etiology

The etiology of this group of diseases is unknown: Immunologic factors have been extensively examined; possible infectious agents have included various enteric bacteria, viruses, and chlamydiae, and attention has most recently focused on mycobacteria; dietary factors (including chemicals and the fiber-poor diet consumed in modern developed countries) have also been considered. Not one of these hypotheses has been proved.

Epidemiology

Since its recognition several decades ago, CD has increased in incidence, not only in Western populations with Northern European and Anglo-Saxon ethnic derivation, but also in third-world populations, blacks, and Hispanics. The disease occurs about equally in both sexes, is more common among Jews, and shows a familial tendency that often overlaps with the occurrence of ulcerative colitis. Most cases begin before age 30, with the peak incidence between 14 and 24.

Pathology

The earliest macroscopic lesions of CD appear to be tiny focal "aphthoid" ulcerations of the mucosa, usually with underlying nodules of lymphoid tissue. Sometimes these lesions regress; in other cases, the inflammatory process progresses to involve all layers of the intestinal wall, which becomes greatly thickened. Changes are most marked in the

submucosa, with lymphedema and lymphocytic infiltration occurring first, and extensive fibrosis later. Patchy ulcerations develop on the mucosa, and the combination of longitudinal and transverse ulcers with intervening mucosal edema frequently creates a characteristic "cobblestone" appearance. The attached mesentery is thickened and lymphedematous; mesenteric fat typically extends onto the serosal surface of the bowel. Mesenteric lymph nodes often enlarge. The transmural inflammation, deep ulceration, edema, and fibrosis are responsible for obstruction, deep sinus tracts and fistulas, and mesenteric abscesses, which are the major local complications.

Segments of diseased bowel are characteristically sharply demarcated from adjacent normal bowel—thus the name "regional" enteritis. Segmental lesions may be separated by normal areas ("skip areas"). The ileum alone is involved in about 35% of cases **(ileitis)**; both ileum and colon, with a predilection for the right side of the colon, are affected in about 45% **(ileocolitis)**; and the colon alone is diseased in about 20% **(granulomatous colitis)**. Occasionally the entire small bowel **(jejunoileitis)** is involved, and rarely also the stomach, duodenum, or esophagus.

Sarcoid-type epithelioid granulomas in the intestinal wall and occasionally in the involved mesenteric nodes are pathognomonic, but since they are absent in up to ½ the patients, they are not essential to diagnose CD. Although they may represent a hidden clue to pathogenesis, they appear to have no definitive bearing on the clinical course.

Symptoms and Signs

Chronic diarrhea associated with abdominal pain, fever, anorexia, weight loss, and a right lower quadrant mass or fullness are the most common presenting features. However, many patients are first seen with an "acute abdomen" simulating acute appendicitis or intestinal obstruction, both of which must be ruled out. Four patterns of regional enteritis occur most often: (1) *inflammation*, characterized by right lower quadrant abdominal pain and tenderness, mimicking appendicitis when acute; (2) *obstruction*, in which intestinal stenosis causes recurrent partial obstruction with severe colic, abdominal distention, constipation, and vomiting; (3) *diffuse jejunoileitis*, with both inflammation and obstruction resulting in malnutrition and chronic debility; and (4) *abdominal fistulas and abscesses*, usually late developments, often causing fever, painful abdominal masses, and generalized wasting. Fistulas may be enteroenteric, enterovesical, retroperitoneal, or enterocutaneous. Obstruction, fistulization, and abscess formation are common complications of inflammation; intestinal bleeding, perforation, and small bowel cancer develop rarely. A history of perianal disease, especially fissures and fistulas, can be elicited in about ⅓ of patients. When the colon alone is affected, the clinical picture may be indistinguishable from ulcerative colitis (see below).

Extraintestinal manifestations fall into 3 principal categories: (1) Complications that often parallel the activity of the intestinal disease and possibly represent acute immunologic or microbiologic concomitants of the bowel inflammation include peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. These manifestations may be reported by over ⅓ of patients hospitalized with inflammatory bowel disease. They are twice as common when colitis is present as when disease is confined to the small intestine. When extraintestinal manifestations occur, they are multiple in about ⅓ of patients. (2) Disorders associated with inflammatory bowel disease but running an independent course include ankylosing spondylitis, sacroiliitis, uveitis, and primary sclerosing cholangitis. The genetic interrelationships among these syndromes, colitis (both ulcerative and granulomatous), and the HLA antigen B27 are discussed under the extracolonic complications of ulcerative colitis, below. (3) Complications that relate directly to the disrupted physiology of the bowel itself are chiefly renal problems. Kidney stones result from disorders of uric acid metabolism, impairment of urinary dilution and alkalinization, and excessive dietary oxalate absorption; UTIs occur especially with fistulization into the urinary tract; and hydroureter and hydronephrosis may ensue from ureteral compression by retroperitoneal extension of the intestinal inflammatory process. Other bowel-

related complications include malabsorption, especially in the face of extensive ileal resection or bacterial overgrowth from chronic small bowel obstruction or fistulization; gallstones, related to impaired ileal reabsorption of bile salts; and amyloidosis, secondary to long-standing inflammatory and suppurative disease.

In children, extraintestinal manifestations frequently predominate over GI symptoms. Arthritis, FUO, anemia, or growth retardation may be a presenting symptom; abdominal pain or diarrhea may be absent. Thus, evaluation of these systemic symptoms in young people must include barium studies of the small bowel and colon, since these may be the only presenting clues to the diagnosis of inflammatory bowel disease.

Diagnosis

CD should be suspected in any patient with the inflammatory or obstructive symptoms described above, and in a patient without prominent GI symptoms who presents with perianal fistulas or abscesses or with otherwise unexplained arthritis, erythema nodosum, fever, anemia, or stunted growth (in a child).

Laboratory findings are nonspecific and may include anemia, leukocytosis, hypoalbuminemia, and increased levels of acute-phase reactants reflected in elevated ESR, C-reactive protein, and/or orosomucoids.

Definitive diagnosis is usually made by x-ray. Barium enema x-ray may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, thickening of the wall, and a narrowed ileal lumen. A small bowel series with spot x-rays of the terminal ileum usually most clearly shows the nature and extent of the lesion. An upper GI series alone, without small bowel follow-through, will almost invariably miss the diagnosis. In advanced cases, the string sign may be seen with marked ileal strictures and separation of bowel loops. In earlier cases, x-ray diagnosis may sometimes be difficult, but techniques of double air-contrast barium enema and enteroclysis may show superficial aphthous and linear ulcers. In questionable cases, fiberoptic colonoscopy and biopsy may help confirm the diagnosis of Crohn's colitis and in many cases may allow direct visualization and biopsy of the terminal ileum. Although CT is proving useful to characterize pathologic changes within the bowel wall and to identify abscesses, it is not routinely needed for initial diagnosis.

Differential Diagnosis

When disease is limited to the colon (granulomatous colitis), differentiation from chronic ulcerative colitis may be difficult, though only about 20% of patients show this strictly colonic distribution. Granulomatous disease is more likely when there is no x-ray or sigmoidoscopic evidence of rectal involvement ("rectal sparing") and when rectal bleeding is absent. Asymmetric involvement of the bowel wall and segmental distribution of lesions on x-ray help to confirm the diagnosis. Severe perianal disease also indicates the presence of granulomatous and not ulcerative colitis.

In diagnosing CD in the small bowel, one must consider other settings in which right lower quadrant disease may resemble granulomatous ileitis. Disease of adjacent organs (eg, appendix and adnexa) may mimic CD. In the acute presentation without a history of chronic bowel symptoms, ileitis may first be diagnosed during surgical exploration for suspected appendicitis. Pelvic inflammatory disease, ectopic pregnancy, and ovarian cysts and tumors may produce right lower quadrant inflammatory signs, and must be ruled out when considering CD in women.

Furthermore, other intrinsic neoplastic, vascular, and infectious bowel diseases may mimic the x-ray picture of CD: carcinoma of the cecum, ileal carcinoid, lymphosarcoma, systemic vasculitis, radiation enteritis, and ileocecal TB. Especially when confronted with an inflamed, edematous terminal ileum and associated mesenteric adenitis during surgery for acute right lower quadrant pain, one must exclude acute *Yersinia enterocolitica* enteritis before labeling a patient with the diagnosis of chronic CD. Although *Yersinia* enteritis is a self-limited infection without chronic intestinal sequelae, the initial clinical picture in both disorders may be indistinguishable, so appropriate serologic and bacteriologic studies

are necessary. In questionable cases, a 3-mo follow-up x-ray of the terminal ileum is most valuable, since complete resolution usually happens by this time with *Yersinia* ileitis, but not with CD.

Prognosis

Complete recovery may follow a single isolated attack of acute ileitis. As noted, however, this self-limited syndrome is usually unrelated to CD and more often due to *Yersinia* infection.

Established chronic CD is characterized by lifelong exacerbations. Growth retardation commonly results when disease occurs during the developmental years. The disease rarely spreads spontaneously without surgical manipulation of the bowel. Fatal complications from free perforation, sepsis, electrolyte imbalance, or inanition are rare; cancer of the digestive tract has lately emerged as the most common cause of CD-related death.

Cancer surveillance: Patients with long-standing CD of the small intestine carry an increased risk of small bowel carcinoma, which may occur in incontinuity bowel as well as in bypassed loops. Furthermore, patients with Crohn's colitis have a long-term risk of colorectal carcinoma, approaching that of ulcerative colitis, given the same extent and duration of disease. Because the reliability of dysplasia as a precancerous marker in CD is not established, there are no uniform guidelines for cancer surveillance.

Treatment

No specific therapy is known. Anticholinergics and diphenoxylate 2.5 to 5 mg, loperamide 2 to 4 mg, deodorized opium tincture 0.5 to 0.75 mL (10 to 15 drops), or codeine 15 to 30 mg, given orally (ideally before meals) up to qid, may relieve cramps and diarrhea. Hydrophilic mucilloids (eg, methylcellulose or psyllium preparations) sometimes help to prevent anal irritation by increasing stool firmness.

Broad-spectrum antibiotics that are active against enteric gram-negative and anaerobic flora may be of benefit in reducing disease activity in some patients but are most effective for suppurative complications (eg, abscess, infected fistula).

Metronidazole 1 to 1.5 gm/day has been shown to be beneficial in CD, especially in Crohn's colitis and has proved particularly useful for treating perianal lesions. Neuropathy manifested chiefly by paresthesias is a common, potentially serious side effect of long-term use; it is usually reversible when the drug is stopped. There is a high incidence of relapse of CD after discontinuing the drug.

Long-term sulfasalazine therapy is useful to suppress low-grade inflammation, especially in the colon, but it is less effective in severe acute exacerbations. It has not been conclusively found helpful in preventing postoperative recurrence. Promising new sulfasalazine analogs provide higher concentrations of 5-aminosalicylic acid **(5-ASA)**, the active ingredient, without any sulfapyridine, which is the moiety responsible for most of the adverse effects of sulfasalazine. (For sulfasalazine therapy, see ULCERATIVE COLITIS, below.)

Corticosteroid therapy is useful in the acute stages of CD. It may dramatically reduce fever and diarrhea, relieve abdominal pain and tenderness, and improve the appetite and sense of well-being. Large doses of oral prednisone, 40 to 60 mg/day, should be given initially. The equivalent dose of hydrocortisone (200 to 300 mg) may be given IV by continuous drip to hospitalized patients who are unable to eat. The dosage is gradually reduced following a satisfactory response so that, by the end of 4 wk, the daily prednisone dosage does not exceed 10 or 20 mg. Although as little as 5 or 10 mg/day may help to control symptoms in some patients, long-term corticosteroid therapy often does more harm than good. Corticosteroids should also be avoided when obvious infections (eg, abscess, fistula) are present. In uncertain cases (eg, those presenting with a tender, inflammatory mass) antibiotics should be given concurrently.

Immunosuppressive drugs: The antimetabolites, azathioprine and 6-mercaptopurine, are effective in CD, especially when it involves the colon. In oral dosage ranging from 1.0 to

2.5 mg/kg/day, they significantly improve patients' overall clinical status, decrease corticosteroid requirements, and often heal fistulas. However, these drugs often do not produce their first clinical benefits for 3 to 6 mo, and side effects of allergy, pancreatitis, or leukopenia must be carefully watched for. Cyclosporine, which shows promise for quicker therapeutic action, is under study. Other immunoregulatory treatments that have been tried or proposed include T lymphocyte apheresis, 4-amino quinolones, and methotrexate, but few controlled studies have been completed. The wide variety of approaches attests to the inadequacy of present-day therapy for this baffling disease.

Some patients with intestinal obstruction or fistula formation have improved on **elemental diets or hyperalimentation,** at least over a short term, and some children have achieved increased rates of growth. Thus, these measures may serve as preoperative or adjunctive therapy, and have been reported from several centers to be valuable as primary therapy.

Surgery is usually necessary when recurrent intestinal obstruction or intractable abscesses or fistulas are present. Resection of the grossly involved bowel may ameliorate symptoms indefinitely but does not cure the disease. The cumulative postoperative recurrence rate, usually at the anastomotic site, is 60 to 95%; ultimately, another operation is required in nearly ½ of cases. Thus, surgery should not be done unless specific complications or failure of medical therapy make it necessary. When operations have been required, however, most patients consider their quality of life to have been improved.

ULCERATIVE COLITIS

A chronic, nonspecific, inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea.

The term "colitis" should be applied only to inflammatory disease of the colon (eg, ulcerative, granulomatous, ischemic, or radiation colitis; bacillary or amebic dysentery). "Spastic" or "mucous" colitis is a misnomer often applied to a functional disorder that is more properly described as "irritable bowel" (see IRRITABLE BOWEL SYNDROME in Ch. 59).

Etiology and Epidemiology

The considerations described for CD (see above) apply equally to ulcerative colitis, except that the evidence for a specific microbial etiology is even less convincing, and the familial tendency is less pronounced. Like CD, ulcerative colitis may afflict patients at any age, but the age-onset curve shows a bimodal distribution with a major peak at ages 15 to 30 and a second smaller peak at ages 50 to 70 that may include some cases of ischemic colitis.

Pathology

The disease usually begins in the rectosigmoid area and may extend proximally, eventually to involve the entire colon, or it may include most of the large bowel at once. **Ulcerative proctitis,** a very common and more benign and limited but often refractory form of the disease, usually remains localized to the rectum, although it too may undergo late proximal spread in about 10% of cases.

Pathologic change begins with degeneration of the reticulin fibers beneath the mucosal epithelium, occlusion of the subepithelial capillaries, and progressive infiltration of the lamina propria with plasma cells, eosinophils, lymphocytes, mast cells, and polymorphonuclear leukocytes. Crypt abscesses, epithelial necrosis, and mucosal ulceration ultimately develop.

Symptoms and Signs

The usual manifestations occur as spells of bloody diarrhea varying in intensity and duration, interspersed with asymptomatic intervals. An attack may be acute and fulminant, with sudden violent diarrhea, high fever, signs of peritonitis, and profound toxemia. More often, an attack begins insidiously, with an increased urgency to defecate, mild lower abdominal cramps, and blood and mucus appearing in the stools.

When the ulcerative process is confined to the rectosigmoid area, the stool may be normal, or hard and dry, but rectal discharges of mucus loaded with RBCs and WBCs accompany or occur between bowel movements. Systemic symptoms are mild or absent. If the process extends proximally, stools become looser and the patient may have 10 to 20 bowel movements/day, often with severe cramps and distressing rectal tenesmus, without respite at night. The stools may be watery and contain pus, blood, and mucus; they frequently consist almost entirely of blood and pus. Malaise, fever, anemia, anorexia, weight loss, leukocytosis, hypoalbuminemia, and elevated ESR may be present with extensive active colitis.

Complications

Hemorrhage is the most common local complication. In **toxic colitis,** a particularly severe local complication, transmural extension of the ulcerative process results in localized ileus and peritonitis. As the toxic colitis progresses, the colon loses muscular tone and within a matter of days or even hours begins to dilate. Plain x-rays of the abdomen show intraluminal gas accumulated over a long, continuous, paralyzed segment of colon, a result of loss of muscle tone. When the diameter of the transverse colon exceeds 6 cm, **toxic megacolon** (or toxic dilation) is present. The severely ill patient has fever to 40° C (104° F), leukocytosis, abdominal pain, and rebound tenderness. *Treatment must be given in the early stages before full-blown megacolon occurs* to avert such dangerous complications as perforation, generalized peritonitis, and septicemia. With prompt, effective treatment, the mortality rate can be held at < 4% but may be > 40% if perforation occurs.

Major perirectal complications such as those seen in granulomatous colitis (eg, fistulas and abscesses) are *not* associated with ulcerative colitis.

Risk of **colon cancer** is increased in patients with long-standing, extensive ulcerative colitis; such patients merit surveillance for early warning signs (see Prognosis, below).

Extracolonic complications include peripheral arthritis, ankylosing spondylitis, sacroiliitis, anterior uveitis, erythema nodosum, pyoderma gangrenosum, episcleritis, and, in children, severely retarded growth and development. The peripheral arthritis, episcleritis, and skin complications often fluctuate with the colitis, whereas the spondylitis, sacroiliitis, and uveitis usually follow a course independent of the bowel disease. Most colitis patients with spinal or sacroiliac involvement also have evidence of uveitis, and vice versa. In fact, these conditions may precede the colitis by many years and may even occur without coexisting bowel disease in relatives of colitis patients. Whether they occur with or without colitis, both ankylosing spondylitis and uveitis have a very strong association with the HLA antigen B27, and genetic overlap is suggested among colitis, spondylitis, uveitis, and the B27 genotype.

While minor changes in liver function tests are common, clinically apparent liver disease may occur in only 1 to 3% of patients. The liver disease may manifest as fatty liver or more seriously as chronic active hepatitis, primary sclerosing cholangitis, or cirrhosis. **Primary sclerosing cholangitis (PSC)** is a complication recognized with increasing frequency, especially in patients who were young when the colitis began. It may antedate symptomatic colitis by many years and is more reliably diagnosed by endoscopic retrograde cholangiography than by liver biopsy. Some investigators believe that signs of subclinical PSC, if systematically sought, could be found in all patients with ulcerative colitis. A late complication of colitis-associated PSC may be **cancer of the biliary tract,** which may appear even 20 yr after colectomy. More than ½ the cases of PSC and cholangiocarcinoma in Western countries occurs in patients with either ulcerative or Crohn's colitis.

Diagnosis

The history and stool examination permit a presumptive diagnosis of ulcerative colitis that should always be supported by **sigmoidoscopy,** which provides a direct, immediate indication of the activity of the disease process. In early cases, the mucous membrane is finely granular and friable, with loss of the normal vascular pattern, and often with scattered hemorrhagic areas; minimal trauma causes bleeding in multiple pinpoint spots. The

mucosa soon breaks down into a red, spongy surface dotted with a myriad of tiny blood- and pus-oozing ulcerations. As the mucosa becomes progressively involved, the inflammatory and hemorrhagic processes extend into the muscular coats of the bowel. Large mucosal ulcerations with copious purulent exudate characterize severe disease. Islands of relatively normal or hyperplastic inflammatory mucosa (pseudopolyps) project above areas of ulcerated mucosa. Even during asymptomatic intervals, the sigmoidoscopic appearance is rarely normal; some mild degree of friability or granularity almost always persists, there is loss of the normal vascular pattern, and biopsy shows evidence of chronic inflammation.

Plain films of the abdomen sometimes help to judge the severity and proximal extent of the colitis by showing loss of haustration, mucosal edema, and absence of formed stool in the diseased bowel. **Barium enema** or total colonoscopy are not usually necessary before treatment begins and may be hazardous in active stages because of risk of perforation. At some point in the course of the chronic disease, however, evaluation of the entire colon should be completed to determine the extent of disease. Total colonoscopy is the most sensitive and widely used method, although barium enema can also be informative. The contrast x-ray examination shows loss of haustration, mucosal edema, minute serrations, or gross ulcerations in severe cases. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is seen in cases of longer duration. Severe perianal disease, rectal sparing, absence of bleeding, and asymmetric or segmental involvement of the colon indicate granulomatous rather than ulcerative colitis.

Colonoscopy with **biopsy** is mandatory to evaluate the nature of a stricture. The endoscopic appearance may also help distinguish ulcerative colitis from CD, but biopsies are rarely helpful in this regard unless a granuloma is seen.

Differential Diagnosis

The importance of excluding an infectious cause of acute colitis before commencing treatment cannot be overemphasized, especially during the first attack. Stool cultures for salmonella, shigella, and *Campylobacter* must be obtained. The presence of *Entamoeba histolytica* should be excluded by examination of fresh, still warm stool specimens, or of colonic exudate aspirated at the time of sigmoidoscopy. Rectal biopsies and serologic titers for amebiasis should also be obtained when a parasitic infection is suspected because of epidemiologic or travel history. History of prior antibiotic use should prompt stool assay for *Clostridium difficile* toxin (see Ch. 58). Especially in the male homosexual, specific infectious proctitis (eg, gonorrhea, herpesvirus and chlamydial infections) should be ruled out (see Ch. 16) and a detailed sexual history should be obtained in all patients. In women using birth control pills, contraceptive-induced colitis is possible; it usually resolves spontaneously after hormone therapy is stopped. In the elderly patient, especially with a history of atherosclerotic heart disease, ischemic colitis should be considered, since it may be the most common cause for colitis in this age group. The x-ray findings of "thumbprinting" and segmental distribution would further suggest this diagnosis. Colon cancer seldom produces fever or purulent rectal discharge but must be excluded as a cause of bloody diarrhea.

Prognosis

A rapidly progressive initial attack may become fulminating in nearly 10% of patients, with complications of massive hemorrhage, perforation, or sepsis and toxemia. Complete recovery after a single attack may occur in another 10% of all patients; in such cases, however, there always remains the possibility of an undetected specific pathogen. Usually, the disease is chronic with repeated exacerbations and remissions.

The incidence of colon cancer is increased when the entire colon is involved and the disease lasts for > 10 yr, independent of disease activity. After 10 yr, the cancer risk of universal ulcerative colitis appears to be about 0.5 to 1%/yr among those patients remaining in the population at risk. Although cancer incidence is highest in cases of universal colitis, the risk is significantly increased with any extent of colitis above the sigmoid colon, even when the entire colon is not involved. There is probably no specifically higher

cancer risk among patients with childhood-onset colitis, independent of their longer durations of disease. Moreover, studies show about 50% long-term survival after diagnosis of colitis-related cancer, a figure no worse than for colorectal cancer in the general (noncolitis) population. Regular colonoscopic surveillance, preferably during remission, is advised for patients whose duration and extent of disease place them at high risk of developing colon carcinoma. Endoscopic biopsies should be taken throughout the colon and submitted for review by an experienced pathologist. The finding of high-grade mucosal dysplasia, or even low-grade dysplasia, in the presence of a macroscopic lesion or mass is a strong indication for colectomy, since the likelihood of concomitant or imminent colorectal carcinoma may be anywhere from 30 to 80%. In such cases, corroboratory pathologic interpretation is important, especially to distinguish between definite neoplastic dysplasia and reactive or regenerative atypia that is secondary to inflammation. Pseudopolyps have no prognostic significance, but may be difficult to distinguish from neoplastic polyps; thus, any polyp that appears suspicious should undergo excision biopsy.

Nearly 1/3 of all patients with extensive ulcerative colitis ultimately require surgery. When performed in time, total proctocolectomy is curative: Both normal life expectancy and normal quality of life are restored.

Patients with localized ulcerative proctitis have the best prognosis. Severe systemic manifestations, toxic complications, or malignant degeneration is unlikely, and late extension of the disease occurs in only about 10%. Surgery is rarely required and life expectancy is normal. The symptoms, however, may prove exceptionally stubborn and refractory. Moreover, since extensive ulcerative colitis may begin in the rectum and then spread proximally, a case should not be definitively characterized as limited proctitis until it has stayed localized for at least 6 mo. Localized disease that extends later often proves to be more severe and more refractory to therapy.

Treatment

Avoidance of raw fruits and vegetables to limit mechanical trauma to the inflamed colonic mucosa may result in symptomatic improvement. A milk-free diet may decrease symptoms in some patients, but need not be continued if no benefit is noted. Anticholinergics or low doses of diphenoxylate 2.5 mg orally bid or tid are indicated for relatively mild diarrhea; higher oral doses of diphenoxylate (5 mg tid or qid), deodorized opium tincture 0.5 to 0.75 mL (10 to 15 drops) q 4 to 6 h, loperamide 2 mg after each loose movement, or codeine 15 to 30 mg q 4 to 6 h may be required for more intense diarrhea. *All these antidiarrheal agents must be used with extreme caution in more severe cases, lest toxic dilation be precipitated.*

In either **mild or moderate disease,** when the colitis does not extend proximally beyond the splenic flexure, remission may sometimes be achieved with instillation of hydrocortisone by enema instead of with oral corticosteroid therapy. Initially, hydrocortisone 100 mg in 60 mL of isotonic saline and methylcellulose is given rectally once or twice/day. It should be retained in the bowel as long as possible; instillation at night, with the patient's hips elevated, may prolong retention and extend distribution. Treatment, if effective, should be continued daily for about 1 wk, then every other day for 1 to 2 wk, then discontinued gradually over 1 to 2 wk. Since systemic side effects may occur as with oral corticosteroids, enema preparations of steroid analogs with less systemic activity are undergoing clinical study. Topical 5-ASA (mesalamine) may also be given in enema form and has proved very beneficial in many cases of refractory proctosigmoiditis and left-sided colitis. The standard dose is 5-ASA 4 gm in 60 or 100 mL of solution given nightly, although more recent studies suggest that 1 gm may be equally effective. Suppositories of 5-ASA 1 gm are also particularly effective in the treatment of proctitis or even proctosigmoiditis, and enjoy greater patient preference. After clinical and endoscopic remission has been established with either preparation (usually within a few weeks), frequency of administration can be tapered, although some long-term maintenance regimen (topical and/or oral) is often required to prevent relapse.

EXHIBIT 1

More extensive **mild or moderate disease** as well as localized disease may respond to sulfasalazine. Since GI intolerance is common, the drug should be given with food, and, if necessary, in the enteric-coated form. Dosage should initially be low (eg, 0.5 gm orally bid) and gradually increased over several days to 3 to 6 gm/day in divided dosage. If a drug rash develops, desensitization may be carried out by beginning with small doses. More serious side effects (eg, blood dyscrasias, hemolytic anemia, paradoxical exacerbation of colitis, and rarely hepatitis) may prevent use of sulfasalazine altogether. New oral analogs of sulfasalazine have been developed to eliminate the sulfapyridine moiety, which is responsible for most of the common side effects, while still allowing delivery of 5-ASA to diseased areas of the small intestine and colon. Olsalazine (Dipentum®) is a 5-ASA compound that, like sulfasalazine, depends upon an azo bond to prevent proximal absorption of the 5-ASA and to keep it in the intestinal lumen until the azo bond is hydrolyzed and active 5-ASA released by the enzymatic action of bacterial flora in the lower ileum and colon. Unlike sulfasalazine, however, which binds 5-ASA to sulfapyridine, olsalazine is a 5-ASA dimer that binds 2 molecules of 5-ASA to each other, so that bacterial cleavage of the compound releases twice the quantity of 5-ASA without any sulfonamide at all. Clinical trials have demonstrated that olsalazine is effective not only to treat mild-to-moderate colitis but also to maintain its remission.

Other forms of 5-ASA consist of the monomeric drug mesalamine with various delayed-release controls. Asacol® is monomeric 5-ASA coated with an acrylic polymer whose pH solubility delays release of the drug until entry into the distal ileum and colon. Claversal® is a similar mesalamine preparation with a pH-dependent acrylic coating that allows release of 5-ASA somewhat more proximally. Pentasa® is a different type of mesalamine formulation in which the 5-ASA is encapsulated in ethylcellulose microgranules that begin timed release of drug much more proximally in the small bowel. Ongoing trials of these preparations are being conducted to determine their optimum dosage and applications in the treatment of both ulcerative colitis and CD. Long-term sulfasalazine therapy (1 gm bid or tid) helps maintain remissions and reduce the frequency of relapses.

Moderately severe disease in ambulatory patients usually requires systemic corticosteroid therapy. Relatively intensive therapy with oral prednisone 40 to 60 mg/day in either single or divided doses frequently induces dramatic remission. After 1 to 2 wk, the daily dose may be gradually reduced by about 5 to 10 mg/wk. Sulfasalazine (2 to 4 gm/day in divided doses) may be added when the colitis is controlled by prednisone at a level of about 20 mg/day; very gradual tapering off and ultimate withdrawal of the corticosteroid may then be possible.

Patients with chronic fecal blood loss may require iron to prevent anemia. If oral iron is not tolerated, parenteral iron may have to be used.

Severe disease, manifested by > 10 bloody bowel movements per day, tachycardia, high fever, or severe abdominal pain, requires hospitalization. If the patient has already been receiving corticosteroid treatment ≥ 30 days at the time of admission, hydrocortisone 300 mg/day should be given by continuous IV drip. In patients who have not received corticosteroids, ACTH 75 to 120 u./day IV given by continuous drip may be the more effective initial therapy, even though adrenal hemorrhage has been reported as a rare complication. In either event, treatment is given for 7 to 10 days while the response is monitored by recording the nature and frequency of bowel movements. An initial abdominal x-ray should be obtained to assess the extent and severity of colonic involvement and the patient must be observed closely for the development of toxic megacolon.

Unless dehydration due to diarrheal losses is imminent, it is usually advisable not to give hydrocortisone or ACTH in IV 0.9% sodium chloride solution, since edema is then a frequent complication. The addition of potassium chloride 20 to 40 mEq/L to the IV fluids usually helps to prevent hypokalemia. Patients with heavy rectal bleeding often require blood transfusions to correct anemia. Parenteral hyperalimentation is sometimes used for nutritional support, but is of no value whatever as primary therapy and should not be allowed to delay definitive surgery (see below).

Oral prednisone 60 mg/day may be substituted after remission has been achieved with the 7- to 10-day course of parenteral treatment. The patient who remains well on the oral regimen for 3 to 4 days may leave the hospital, and corticosteroid dosage may be gradually reduced at home under close medical supervision.

Azathioprine, 6-mercaptopurine, and cyclosporine have been used in the treatment of ulcerative colitis, but their long-term risk/benefit ratios have not been clearly established.

Toxic colitis *is a grave emergency.* As soon as signs of toxic colitis or impending toxic megacolon are detected, the following steps should be taken immediately: (1) Discontinue all antidiarrheal drugs; (2) give nothing by mouth and pass a long intestinal tube attached to intermittent suction; (3) give aggressive IV fluid and electrolyte therapy, with 0.9% sodium chloride, potassium chloride, albumin, and blood as needed; (4) give ACTH 120 u./day or hydrocortisone 300 mg/day by continuous IV drip; and (5) give antibiotics (eg, ampicillin 2 gm IV q 4 to 6 h, or cefazolin 1 gm IV q 4 to 6 h).

Having the patient roll over in bed from the supine to prone position q 2 to 3 h may help redistribute colonic gas and prevent progressive distention. Passage of a soft rectal tube may also be helpful in some cases, *but it must be done with extreme caution to avoid bowel perforation.*

The patient must be watched closely for signs of progressive peritonitis or perforation. Percussion over the liver is important, since loss of hepatic dullness may be the first clinical sign of free perforation, especially in the patient whose peritoneal signs are suppressed by massive corticosteroid dosage. Abdominal x-rays should be obtained at least daily to follow the course of colonic distention and to detect free air. If intensive medical measures do not produce definite improvement within 24 to 48 h, immediate surgery is required or the patient may die from perforation and attendant sepsis.

Surgery: Emergency colectomy is indicated for massive hemorrhage, fulminating toxic colitis, or perforation. Subtotal colectomy with ileostomy and rectosigmoid mucous fistula is usually the procedure of choice, since total proctocolectomy with abdominoperineal resection is more than most critically ill patients can tolerate.

The rectosigmoid stump may then be electively removed later or may be used for mucosal stripping and ileorectal "pull through" procedures with or without intrapelvic intestinal reservoirs. In any event, the intact rectal stump should not be allowed to remain indefinitely because of the risk of disease activation or subsequent malignant degeneration.

Elective surgery is indicated for high-grade mucosal dysplasia or clinically suspected carcinoma, for all symptomatic strictures, for growth retardation in children, or most commonly for intractable chronic disease resulting in invalidism or high-dose steroid dependence. Rarely, severe colitis-related extraintestinal manifestations (eg, pyoderma gangrenosum) may also be indications for surgery.

Total proctocolectomy permanently cures chronic ulcerative colitis. Permanent ileostomy has been the traditional price of this cure, although various alternatives (eg, the continent ileostomy or especially endorectal "pull-through" procedures) are usually chosen. The cosmetic details of the surgery are less critical than the curative nature of colectomy in a disease as serious as ulcerative colitis. Nonetheless, the physical and emotional burdens imposed by any form of colon resection must be recognized, and care should be taken to see that the patient receives all the logistic instructions and psychologic support that are so necessary both before and after surgery.

---

58. ANTIBIOTIC-ASSOCIATED COLITIS

An acute inflammatory bowel disorder associated with antibiotic use that encompasses a spectrum from transient mild diarrhea to a severe colitis marked by exudative mucosal plaques ***(pseudomembranous colitis).***